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Odor localization in structural interhemispheric deficits

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Contrary to all other sensory systems, olfactory information is processed predominantly ipsilaterally. Furthermore, odor localization, based on inter-nostril differences, is usually not possible under controlled conditions. These two observations suggest information exchange between both cerebral hemispheres in the olfactory system, although the exact anatomical substrate remains unknown. This study aimed to identify the anatomical structures necessary for odor localization, with a particular focus on the role of interhemispheric communication. We assessed the ability to localize pure olfactory and mixed olfactory/trigeminal stimuli in 6 participants with structural interhemispheric deficits (including surgical transection or agenesis of the corpus callosum (CC) and agenesis of the CC and anterior commissure (AC, one case)) and compared their performance to 46 healthy controls. Of the six participants with structural interhemispheric deficits, three were unable to localize either stimulus. Two participants performed significantly better than chance for both pure and mixed stimuli, while one participant exhibited the typical localization pattern observed in most controls—accurate localization of the mixed olfactory/trigeminal stimulus but inability to localize the pure olfactory stimulus. Our results suggest that localization of chemosensory stimuli relies, at least in part, on CC, highlighting its role in interhemispheric communication for olfactory processing. The varying odor localization performance observed in participants with agenesis of CC indicates that compensatory mechanisms may be promoted in some cases, potentially preserving normal localization functions despite the absence of major commissural pathways.

Key words: olfaction, trigeminal system, lateralization, commissural deficits, structural connectivity.

Introduction

The corpus callosum (CC) is the major bundle of commissural fibers connecting the two hemispheres of the brain, enabling the exchange of cognitive, motor, and sensory information. Alongside the CC, the anterior commissure (AC) also plays a crucial role in interhemispheric communication, particularly in connecting regions involved in olfactory and limbic functions. While the CC's involvement in integrating sensory inputs, such as vision and auditory cues, has been well documented, its involvement in chemosensory processing remains unclear.

Several medical conditions can compromise the integrity of the CC, leading to varying degrees of neurological dysfunction. One such condition is agenesis of the corpus callosum (AgCC), a brain malformation where the CC is partially or entirely absent due to disruptions during fetal development. AgCC is one of the most common brain malformations (Kolodny 1989), with an estimated prevalence between 1.8 and 2.5 per 10,000 live births (Glass et al. 2008; Ballardini et al. 2018). Causes of AgCC range from maternal alcohol consumption to genetic factors influencing commissural axon guidance (Hofman et al. 2020). The neurological and cognitive consequences of AgCC vary, with symptoms ranging from mild behavioral issues to severe neurological deficits (Edwards et al. 2014). In addition to congenital conditions, medical interventions may also affect the CC, such as callosotomy, a surgical procedure used to treat severe and pharmacologically unresponsive epilepsy. By severing the CC, callosotomy disrupts communication between the cerebral hemispheres (Corballis and Corballis 2001), often resulting in impairments in sensory and motor integration (Mancuso et al. 2019), as well as altered functional connectivity (Roland et al. 2017). Most sensory systems process information in the hemisphere contralateral to the side of stimulus. Some cognitive functions also tend to be specialized in one hemisphere to maximize for cortical space (Geschwind and Galaburda 1985). Patients who have undergone callosotomy may struggle to perform tasks requiring the coordination of both hemispheres (Gazzaniga 2000), such as writing with their left hand (Lassonde and Ouimet, 2010)—writing is mostly specialized in the left hemisphere (Gur et al. 1984) whereas movement of the left hand is controlled by the right

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hemisphere. It is noteworthy that late callosotomized patients tend to show less compensatory neural reorganization than individuals with AgCC (Lassonde et al. 1991), which amplifies the effects of this disconnection.

The absence of the CC has been shown to affect sensory integration for most modalities, such as vision and hearing, which rely on interhemispheric communication. For example, the CC plays a role in spatial attention and hand-eye coordination (Hines et al. 2002). Absence of CC can cause various vision impairments due to an improper integration of the two halves of our vision field (Berlucchi and Rizzolatti, 1968; Antonini et al. 1979; Pietrasanta et al. 2012). Acallosal individuals can also exhibit difficulty to localize sounds based on interaural differences (Lessard et al. 2002; Hausmann et al. 2005; Dias et al. 2020). However, the effects of CC absence on chemosensory processing, particularly in olfaction, are not well understood.

In some cases of AgCC, AC is also absent. The AC is another critical commissural structure, facilitating the transfer of information between olfactory and limbic regions across hemispheres. Specifically, the AC connects the anterior olfactory nuclei (AONs) from both hemispheres, playing a key role in relaying signals between the olfactory bulbs and piriform cortex (PC), which are essential for processing olfactory information (Haberly and Price 1978; Reyher et al. 1988; Illig et al. 2009; Dalal et al. 2020). This interhemispheric communication mediated by the AC ensures that sensory input from one OB can be integrated and processed across both hemispheres to the contralateral OB, contributing to a unified olfactory perception.

Enlargements of the AC observed in some individuals with AgCC (Wolf et al. 2011) suggest its involvement in early compensatory mechanisms (Barr and Corballis 2002). Supporting this, AC can facilitate complex interhemispheric transfer of multisensory information, including visual, auditory, and olfactory signals (Risse et al. 1978) in patients with complete CC sections. Together, these findings suggest that in the absence of the CC, the AC plays a compensatory role by preserving interhemispheric communication, especially for olfactory processing. In turn, the absence of the AC itself may significantly impair this communication, potentially leading to altered olfactory perception due to disrupted signal integration between olfactory regions. When both CC and AC are absent, however, interhemispheric communication may be severely compromised, potentially resulting in more pronounced deficits in olfactory processing.

Unlike other sensory systems, the olfactory system mainly has ipsilateral projections in the brain (Hummel et al. 1995; Lundström et al. 2011). In other sensory systems, bilateral information is integrated in a way that allows for the localization of stimuli (e.g. identifying where a sound is coming from or the spatial orientation of visual objects). However, olfactory processing does not support such localization. While olfactory information is primarily processed ipsilaterally, some bilateral communication occurs (Dalal et al. 2020; Davis and Macrides 1981), and the input from both nostrils is merged into a unified olfactory percept. This makes it difficult to discern from which nostril a specific scent originated; in other words, the human olfactory processing apparatus does not allow for lateralization of stimuli based on inter-nostril differences (Kobal et al. 1989; Frasnelli et al. 2009). Some studies have reported the ability of the olfactory system to localize pure odorants (von Békésy 1964; Porter et al. 2005); however, this ability appears to be variable and, in most cases, not reliably possible (Doty et al. 1978; Kobal et al. 1989; Radil and Wysocki, 1998; Frasnelli et al. 2009; Kleemann et al. 2009). The bilateral integration of olfactory stimuli that forms unified odor percepts is thought to rely on the AC, connecting olfactory regions to their homologous structure across hemispheres (Haberly and Price 1978; Brunjes 2013). As a consequence, disruption of the AC should interfere with this mechanism and therefore allow for localization of olfactory stimuli.

In this context, it is important to point out that, in addition to olfaction, volatile stimuli from our environment are perceived through the trigeminal system, an additional chemosensory system, associated with the trigeminal nerve (CNV). More specifically, the trigeminal system is responsible for sensations such as irritation, freshness, and warmth (Doty et al. 1978; Laska et al. 1997; Frasnelli et al. 2011a). In fact, most odorants stimulate both the olfactory and trigeminal systems and are therefore called mixed olfactory-trigeminal stimuli. In contrast to pure olfactory stimulation (e.g. with phenyl ethyl alcohol [PEA]), trigeminal stimulation (e.g. with eucalyptol [EUC]) allows for localization through inter-nostril differences (Doty et al. 1978). The CC is expected to play a key role in this process by transferring sensory information between hemispheres, enabling the brain to compare signals from each nostril. Disruption of the CC should interfere with this mechanism and consequently impair the localization of mixed olfactory-trigeminal stimuli.

This study aims to investigate how the absence of key interhemispheric pathways—the CC and AC—affects the ability to localize both pure olfactory and mixed olfactory-trigeminal stimuli. We predict that patients with AgCC and absent AC will demonstrate altered odor localization abilities. More specifically, we hypothesize that the absence of CC and/or AC enables for the localization of pure odorants, which is typically not possible in normal olfactory processing. In turn, for trigeminal stimulation, which activates both ipsilateral and contralateral pathways in the brain (Iannilli et al. 2008; Albrecht et al. 2010), CC integrity is crucial to localize trigeminal odorants. We therefore hypothesize that the absence of CC and/or AC impairs the localization of mixed olfactory-trigeminal stimuli. We expect this effect to be more pronounced for the left nostril, as the right nostril is superior in trigeminal localization tasks (Frasnelli et al. 2009).

Materials and methods

Participants

All participants provided informed written consent to participate in the study according to the Declaration of Helsinki. The study was approved by the Ethics Board of the Faculty of Arts and Science at the Université de Montréal (CERFAS) (Certificate #CERFAS-2012-13-077-D).

We included a total of six individuals with absence of CC (Table 1). Four of them presented congenital agenesis of CC, one presented combined congenital agenesis of CC and AC, whereas the sixth participant had undergone a surgical callosotomy at age 22, sparing the AC. Some of these individuals had previously participated in other studies (Sauerwein et al. 1981; Sauerwein and Lassonde 1983; Lassonde et al.

Table 1. Summary of patients' general information and structural interhemispheric deficit.

	Age	Sex	Handedness	Corpus callosum	Anterior commissure	IQ	Schooling years	Employment
MG	44	M	L	Agenesis	Preserved	77	11	Unemployed
LG	52	F	R	Agenesis	Preserved	78	11	Janitor
SG	53	F	R	Agenesis	Preserved	84	11	Nurse aide
SP	48	M	R	Agenesis	Absent	107	13	Assistant manager
MD	25	F	Not assessed	Agenesis	Preserved	n/a	15	Student
ML	37	M	L	Callosotomy		76	11	Unemployed

Summary of demographic characteristics and structural interhemispheric deficits in patients included in the study. Information includes age, sex, handedness, status of the CC and AC (as assessed by neuroimaging), IQ, years of formal education, and current employment. "Agenesis" refers to complete absence of the CC, while "Callosotomy" indicates a surgical disconnection. "Preserved" or "Absent" describes the integrity of the AC. IQ data are not available (n/a) for patient MD.

1988, 1991). Their results were compared to those of 46 healthy participants.

Experimental group

MG.

Case MG is a 44-yr-old left-handed male. He was first evaluated by a neurologist at age 4 for prolonged enuresis, poor motor coordination, and delayed language acquisition. Agenesis of the CC was confirmed at age 8 using CT scan and MRI; his AC is preserved. His intelligence quotient (IQ) is 77 (Ottawa-Wechsler scale). He completed 11 yr of schooling and was unemployed at the time of testing.

LG.

Case LG, MG's sister, is a 52-yr-old right-handed female. She was born prematurely (7th mo of gestation) and was diagnosed with agenesis of the CC at age 8 after presenting with mutism and ataxia; her AC is preserved. Her IQ is 78 (Ottawa-Wechsler scale). She completed 11 yr of schooling and employed as a janitor at the time of testing.

SG.

Case SG, another sibling of MG and LG, is a 53-yr-old right-handed female. Like her siblings, she was born following a breech delivery. She exhibited delayed motor milestones, including walking and some motor incoordination. She was only diagnosed with agenesis of the CC when she was recruited, together with her parents, for a scientific study on agenesis of the CC (Lassonde et al. 1991). Her AC is intact. Her IQ is 84 (WAIS-R), and she completed 11 yr of schooling. She was employed at a retirement home at the time of testing.

SP.

Case SP is a 48-yr-old right-handed male. He was born with hypertelorism and cleft lip and palate, which was surgically corrected at 4 mo of age. He further suffered from a basal transpalatal encephalocele, which was surgically removed by bifrontal craniotomy at 18 mo. It was on this occasion that agenesis of both the CC and the AC was diagnosed. His posterior commissure is intact. Further surgical interventions included correction of a left hydrocele (at age 4) and 2 prepalatal fistulas. He further suffers from growth retardation, hypothyroidism, and hypopituitarism. He has an IQ of 107 (WAIS-R) and completed 13 yr of schooling. He was employed as an assistant manager in a drug store at the time of testing.

MD.

Case MD is a 25-yr-old woman. She had an inconspicuous development, and agenesis of the CC was diagnosed as an incidental finding during participation in a previous study using MRI. Both anterior and posterior commissure are preserved. Her IQ was not assessed; at the time of testing, she was a university graduate student in management.

ML.

Case ML is a 37-yr-old left-handed male. Throughout childhood and adolescence, he suffered from epileptic seizures; at age 22, a complete callosotomy was performed. He has an IQ of 76 (WAIS-R) and completed high school. He was unemployed at the time of testing.

Control group

We also included a total of 46 control participants (23 men and 23 women; mean age: 27.4 (8.2) yr, range: 18 to 53 yr), some of whom had participated in earlier studies (Frasnelli et al. 2009). While their IQ and level of education were not formally assessed, most were university students. All control participants had no known history of neurological and psychiatric condition.

Procedure

We assessed participants' abilities to localize monorhinally presented stimuli as described in previous studies (Frasnelli et al. 2009), using two distinct stimuli. Specifically, we used phenyl ethanol (PEA), which has a rose odor and is a relatively pure olfactory stimulus (Doty et al. 1978) as well as eucalyptol (EUC), a eucalyptus-scented compound that also stimulates the trigeminal system by evoking a cooling sensation. Glass bottles were filled with 5 ml of pure stimulus. We tested both stimuli separately. During testing, participants moved 2 bottles (one containing the stimulus and the other containing 5 ml of odorless solvent propylene glycol) to their nostrils, with one bottle to the left and the other to the right nostril. Participants took one sniff, ensuring that the air from the headspace of each bottle reached into its corresponding nostril. After exposure to each stimulus participants nonverbally identified to which nostril the stimulus had been presented by raising the corresponding hand. A total of 40 stimuli were presented to blindfolded participants at an interstimulus interval of approximately 40 s, resulting in a total testing time of about 26 min. Stimulation of the left or right nostril followed a pseudo-randomized and

counterbalanced sequence; each nostril was stimulated 20 times.

Statistics

We calculated the difference from chance level by using one-sample *t*-tests. We further computed a repeated measures ANOVA with *stimulus* (eucalyptol, PEA) as within within-subject factor and *group* (patients, controls) as between-subject factor to examine the effects of these variables on localization scores.

Sensitivity (d') and response bias (criterion C) were calculated, according to Signal Detection Theory, for each participant based on a 2-alternative forced-choice odor localization task (left vs. right) across two odor conditions (PEA and eucalyptol). d' was derived as a measure of the ability to distinguish between left and right odor presentations, and criterion C assessed the tendency to favor one response over the other, independent of sensitivity. Group comparisons (controls vs. patients) and condition comparisons (PEA vs. eucalyptol) were conducted using the Mann–Whitney U test (Wilcoxon rank-sum).

Next, we determined, by means of a binomial distribution, the threshold above/below of which performance can be assumed to be different from chance. For a 40-items, 2-forced-choice paradigm, scores below 14 and above 26 are considered to be different from chance (binomial, $P < 0.05$). Nostril-specific performance was also assessed individually; for a 20-items, 2-forced-choice paradigm, scores below 6 and above 14 were considered to differ significantly from chance (binomial, $P < 0.05$).

Results

Participants' scores are presented in Fig. 1.

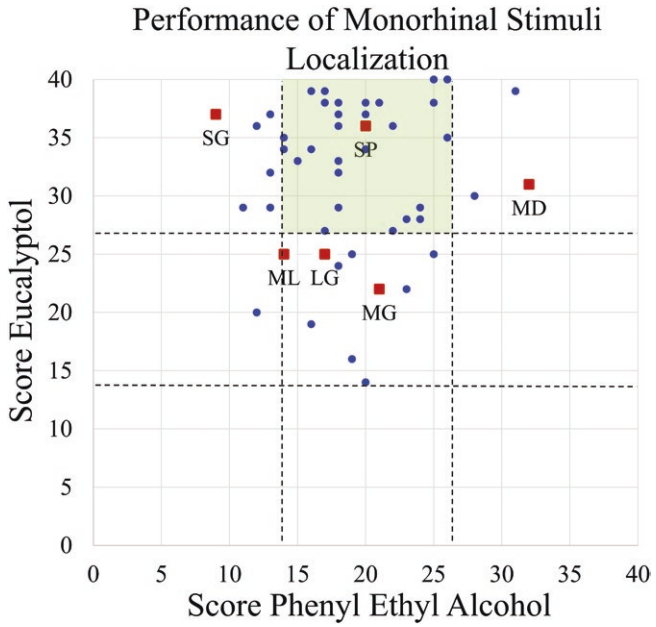

Fig. 1. Performance patterns of odor localization for phenyl ethanol and eucalyptol for control participants (dots) and patients (squares). The green box highlights scores over chance for eucalyptol (>26) and by chance for phenyl ethanol (between 14 and 26), which are the expected values for normal localization performance. Anything outside the green box is considered as abnormal performance. All patients but one performed outside normal values.

Control participants reached, on average, a sensitivity (d') of −0.06 when localizing PEA and 1.47 when localizing EUC. This score was significantly different from 0 for EUC (one-sample *t*-test; $P < 0.001$), but not for PEA ($P = 0.434$). Similarly, the patient group's d' was −0.06 when localizing PEA and 1.06 when localizing EUC. Again, these scores were significantly different from chance for EUC ($P = 0.025$), but not for PEA ($P = 0.872$) (Fig. 2). The ANOVA revealed a significant effect of stimulus (F (1.50) = 110.2; $P < 0.0001$), but no significant effect of group.

Based on binomial distribution, the majority of control participants (38/46; 82%) performed significantly different than chance (all above chance) in the trigeminal localization task, while only 8/46 (17%) performed significantly different than chance (2 above chance, 6 below chance) in the olfactory task. In the patient group, 3/6 (50%) performed significantly different than chance (all above chance) in the trigeminal localization task, and 2/6 (33%) performed significantly different than chance (1 above chance, 1 below chance) in the olfactory task. When combining both stimuli, 15/46 (32%) controls showed a pattern that deviated from expectation, i.e. at-chance performance for olfactory localization and above-chance performance for trigeminal localization. In contrast, the majority of patients (5/6; 83%) (Fig. 1) showed such a deviation from the expected pattern. These distributions were significantly different from each other (chi-square; $P = 0.017$).

As a next step, we investigated a response bias (criterion C). The control group exhibited a negative C, significantly different from 0, for both PEA (−0.23; $P = 0.003$) and EUC (−0.21, $P = 0.015$). Similarly, the patient group exhibited a nominal bias to the right nostril, i.e. a negative C, for both stimuli (PEA: −0.22; EUC: −0.05), which nevertheless were not significantly different from 0 (PEA: $P = 0.266$; EUC: $P = 0.828$). A repeated measures ANOVA did not yield any significant effect of group or stimulus.

Therefore, as a next step, performance for the olfactory (PEA) and mixed olfactory-trigeminal (EUC) stimuli were analyzed separately for each nostril. Nostril-specific performance for each group and condition are summarized in Table 2. For the olfactory stimulus (PEA), control participants performed below chance with the left nostril and at chance with the right nostril, showing a significant nostril difference ($P = 0.001$). In contrast, patient scores were not significantly different from chance for either nostril, with no nostril difference ($P = 0.477$), but there was no significant difference between patient and control nostril performance distributions (Mantel–Haenszel test; $P = 0.634$). For the mixed olfactory-trigeminal stimulus (EUC), both nostrils in controls scored above chance with no nostril difference ($P = 0.085$). Patients scored above chance for the right nostril but not for the left nostril, and no nostril difference was observed ($P = 0.760$). The difference between nostril performance distributions in patients and controls failed to reach significance (Mantel–Haenszel test; $P = 0.058$).

Finally, we subdivided the patient group according to their type of interhemispheric deficit (CC agenesis and callosotomy). Of the five patients with complete CC agenesis, all but one (4/5; 80%) exhibited abnormal performance patterns. In fact, two patients had impaired trigeminal localization, while the other two showed abnormal performance with olfactory localization. Specifically, MG and LG could localize neither EUC nor PEA differently from chance. Conversely,

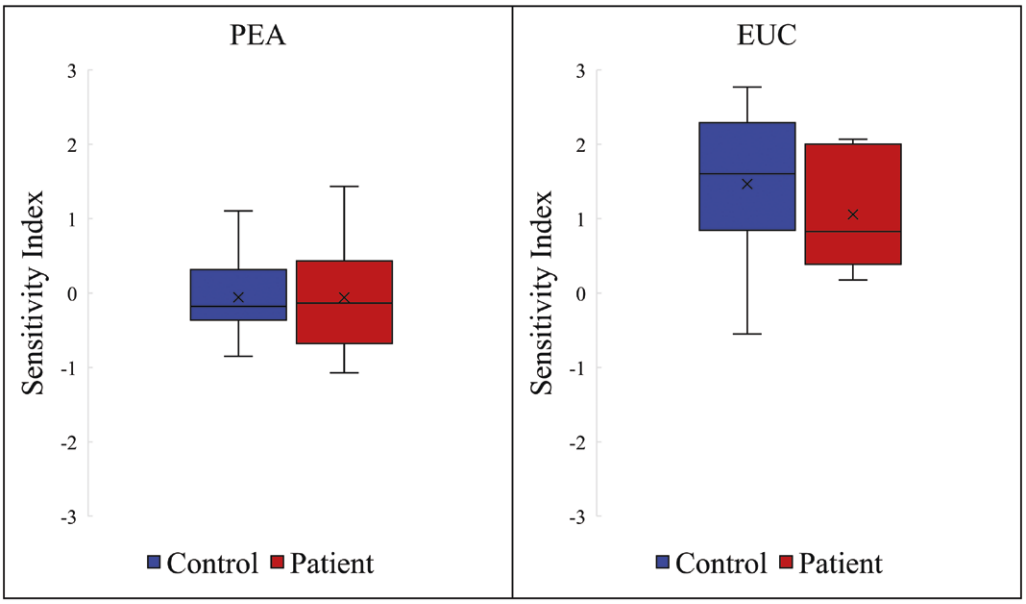

Fig. 2. Analysis of sensitivity (d') of odor localization for phenyl ethanol and eucalyptol for control participants (left) and patients (right). Mann–Whitney *U* test revealed a significant effect of stimuli (control: $P = 2.186e\text{-}12$; patient: $P = 0.026$) but did no difference between groups (PEA: $P = 0.774$; EUC: $P = 0.223$).

Table 2. Nostril-specific performance of odor localization.

Stimulus	Group	Left Nostril Mean ± SD *t*-test vs 0	Right Nostril Mean ± SD *t*-test vs 0	Nostril Difference (*P*)	Proportion of participants with scores different than chance (left nostril/right nostril)
PEA	Controls	8.5 ± 3.3 $P = 0.004^{**}$	10.9 ± 3.6 $P = 0.1$	$P = 0.001^{**}$	20%/21%
	Patients	8.5 ± 2.8 $P = 0.25$	10.3 ± 5.4 $P = 0.89$	$P = 0.48$	17%/33%
EUC	Controls	15.3 ± 4.2 $P < 0.001^{***}$	16.7 ± 3.7 $P < 0.001^{***}$	$P = 0.085$	63%/78%
	Patients	14.3 ± 3.9 $P = 0.058$	15.0 ± 3.4 $P = 0.021^{*}$	$P = 0.76$	33%/78%

Nostril-specific odor localization performance for control participants and patients with interhemispheric deficits. Mean ± SD scores are shown separately for left and right nostril stimulation with PEA (a pure olfactory stimulus) and eucalyptol (EUC, a mixed olfactory-trigeminal stimulus). One-sample *t*-tests were conducted to compare performance against chance level (0), and paired *t*-tests assessed performance differences between nostrils. The final column indicates the proportion of participants in each group whose performance exceeded chance level for each nostril. ($^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$).

both MD and SG could localize EUC, with MD also able to localize PEA while SG performed significantly *below* chance for PEA localization (i.e. consistently localized to the wrong side). SP was the only patient with CC agenesis to display a normal performance pattern, i.e. correctly lateralizing EUC stimulations, at-chance performance for PEA. In this context it is important to point out that SP was the only patient with AgCC *and* absence of AC. ML, the only callosotomy patient, exhibited an at-chance performance to localize both EUC and PEA.

Discussion

Our study aimed to identify the anatomical substrates of odor localization by examining how absence of CC and/or AC affects the ability to localize (1) a pure odorant and (2) a mixed olfactory-trigeminal stimulus. We found that the absence of CC (in one case the absence of CC and AC) results in variable performance patterns in monorhinal localization tasks. The absence of CC (or CC and AC) does not produce uniform effects, highlighting the complex role of interhemispheric communication in olfactory processing.

Olfactory information is primarily processed ipsilaterally (Hummel et al. 1995). The disruption of interhemispheric communication may potentially isolate olfactory input to one brain hemisphere, allowing for the lateralization of pure odorants—an ability typically not possible in healthy individuals. Contrary to our expectations, our results showed that the absence of the CC did not facilitate olfactory localization; 4/6 patients performed at chance for the localization of a pure odorant. Among the remaining patients, one correctly localized the odorant, while the other consistently mislocalized the odorant to the opposite side. However, across all patients, performance was not significantly different from the control group, suggesting that CC absence does not inherently enable localization of pure odorants.

The AC participates in transfer of olfactory information between hemispheres by connecting olfactory structures between hemispheres (Dalal et al. 2020). It might therefore support interhemispheric communication more effectively than the CC alone in olfactory processing and be responsible for the uniform bilateral perception of pure odors. However, SP, a patient with CC agenesis *and* AC absence, exhibited normal localization results for the pure odorant, indicating that even the concurrent absence of both commissures does not enable localization of pure odorants. This suggests that AC involvement in odor localization is complex and may require a larger sample size to be fully understood.

Interestingly, ML, a patient who underwent callosotomy at age 22, was also unable to localize the pure odorant, suggesting that neither surgical absence of the CC nor developmental agenesis enables pure odorant localization. In healthy individuals, regular exposure to an odorant increases olfactory sensitivity (Dalton et al. 2002) and olfactory training can develop the ability to localize odors (Negoias et al. 2013). This suggests that while interhemispheric communication alone does not prevent localization of pure odors, it may be essential for developing this ability by simultaneously maintaining the typical nonlocalization of pure odors. This balance could also be mediated by interactions taking place at the mucosal level. The olfactory system appears to interact with the trigeminal system at the peripheral level (Tremblay and Frasnelli 2018); however, the mechanisms driving this interaction are still not well understood, and they may potentially play a role in the localization of odors. Further research is needed to explore the role of these peripheral mechanisms in odor localization.

Trigeminal processing typically involves contralateral pathways, utilizing the pain network (May 2007; Tracey, 2008; Seifer and Maihofner, 2009; Albrecht et al. 2010). In contrast to cutaneous trigeminal stimuli, which mostly activate contralateral brain regions, intranasal chemical stimuli also produce a strong ipsilateral activation in the thalamus (Iannilli et al. 2008). These findings suggest that trigeminal processing involves ipsilateral pathways, similarly to the olfactory system, as well as contralateral pathways. We predicted that the AgCC and callosotomy would interfere with the ability to localize mixed olfactory-trigeminal stimuli. However, the absence of the CC influenced the localization of a mixed olfactory-trigeminal stimulus differently among participants. While 3/6 patients could not localize a mixed olfactory-trigeminal stimulus better than chance, the overall distribution failed to significantly differ from controls. While a larger sample size may have yielded a significant difference, this suggests that interhemispheric communication is involved in trigeminal localization, but the absence of the CC does not uniformly disrupt this process, potentially due to compensatory mechanisms involving other commissural fibers. This is in line with the notion that individuals without CC are known to present symptoms and clinical conditions of varying nature and intensity (Hofman et al. 2020).

Notably, for trigeminal stimuli, right-nostril performance tended to be above chance more often and mean performance was significantly different from chance, regardless of overall bilateral performance, whereas stimuli presented to the left nostril seemed more affected and mean performance was not different from chance. Previous findings also showed better performance in localization of stimuli presented to the right nostril in healthy subjects combined with a rightward tendency (Frasnelli et al. 2009). This characteristic seems to be preserved in structural interhemispheric deficits. Due to the relatively small sample size in the patient group, it is still unclear whether this tendency is accentuated by the lack of interhemispheric communication or remains unchanged. The lack of significant difference between left vs right nostril performance in the patient group and the control group suggests that abnormal interhemispheric transfer does not exacerbate the intrinsic right-nostril advantage. Moreover, both groups share a similar sensitivity (*d'*) and response bias (*C*), meaning the difference in nostril performance in the patient group could possibly reach significance with a larger sample size, such as in the control group.

This tendency did not manifest as strongly for olfactory localization. Only one patient showed discrepancies between nostril performance. Patient MD effectively localized stimuli presented to the right nostril but performed at-chance for the left nostril. This aligns with prior findings that the right nostril stimuli produce stronger activation and better discrimination in olfactory tasks (Zatorre and Jones-Gotman, 1990; Savic and Gulyas 2000). Olfactory performance was not dependent on nostril side across all patients and no difference appeared between nostrils in the absence of AC. In the control group, overall olfactory performance between nostrils was significantly different in favor of the right nostril. Surprisingly, disruption of interhemispheric communication could possibly minimize rightward dominance for olfactory localization. Once again, however, *d'* and *C* were not different between controls and sensitivity, suggesting that a lack of statistical power may explain the missing effect in the patient group.

Previous studies highlighted the involvement of the AC and subcortical commissures in interhemispheric transfer of olfactory and trigeminal information. For instance, anterior olfactory nucleus (AON) neurons reference both nostrils to distinguish odor source sides (Kikuta et al. 2010), and the AC mediates communication between AONs (Dalal et al. 2020). In rodents, anterior PC neurons have been shown to integrate both ipsilateral and contralateral olfactory inputs, with some neurons selectively responding to unilateral or bilateral stimulation (Wilson 2017). This suggests that commissural connections play a role in birhinal odor processing, which may be relevant for inter-nostril comparisons involved in odor localization. These results support the idea that impaired commissural pathways could disrupt the integration of olfactory inputs and affect odor localization. However, our findings show that, in humans, absence of both the CC and AC does not prevent normal performance for localization of a mixed olfactory-trigeminal or pure olfactory stimulus, suggesting other compensatory pathways might be at play. These results underscore the need for further studies to elucidate the precise roles of these structures in odor localization.

Furthermore, peripheral interactions between the olfactory and trigeminal systems might influence localization performance. The two systems modulate each other's sensory perceptions in an excitatory-inhibitory manner, where trigeminal stimuli can suppress olfactory perceptions (Cain et al. 1980), and anosmia alters trigeminal sensitivity (Hummel et al. 2003), but results in higher peripheral electrophysiological response to stimuli (Frasnelli et al. 2007). Given EUC's property as a mixed olfactory-trigeminal stimulus, its localization involves both systems. This supports the need for more research

into their interaction, potentially incorporating both peripheral and central electrophysiological recordings to explore the mechanisms underlying this interaction in odor localization.

Patients with callosotomy, especially when the intervention is performed later in life, may not benefit from compensatory mechanisms of the same magnitude as observed in individuals with developmental CC agenesis (Lassonde et al. 1991). While younger patients can rely on ipsilateral pathways to preserve interhemispheric integration (Lassonde et al. 1986), this capacity may be reduced in older individuals with functionally mature CCs. The inability to localize EUC of the one patient with callosotomy points to the importance of developmental plasticity in preserving normal function. AgCC patients, lacking the major commissural fiber bundle, might engage different intrahemispheric plasticity processes, as seen in functional recovery from supplementary motor area syndrome, where AgCC patients can recover through intrahemispheric adaptation (Obaid et al. 2022) instead of the usual recovery mechanisms involving callosal fibers (Vassal et al. 2017). This may explain the wider range of effects observed in AgCC, which can vary from asymptomatic to severely impaired (Hofman et al. 2020), compared to postsurgical callosotomy, which is more prone to present with disconnection deficits such as disconnection syndrome (Lassonde et al. 1991, 1995; Sauerwein and Lassonde 1997). Future studies should adopt a longitudinal approach to investigate the evolution of neural plasticity and compensatory mechanisms in olfactory-trigeminal processing over time.

This study has some limitations. First, three participants with AgCC were from the same family. While this could raise concerns about independent sampling, their performance does not appear to be clustered in a way that would suggest a systematic familial influence. While the small sample size limits the generalizability of our findings, recruiting six participants with structural interhemispheric deficits is, in itself, a strength, given the rarity of this condition. While sex-related differences play a role in olfactory processing, our small experimental sample size (three males, three females) prevented a meaningful analysis. However, sex-dependent effects in the control group were previously examined by Frasnelli et al. (2009) and did not yield a significant difference for localization. Next, the unique variability in clinical presentations among these individuals may have influenced performance patterns, making it challenging to draw definitive conclusions. Furthermore, some participants with AgCC or callosotomy exhibited lower IQ and disinhibited behavior, characterized by impulsive verbal responses and difficulty filtering thoughts. While these cognitive and behavioral factors did not invalidate the findings due to the simplicity of the task and procedure (identifying left or right side), they should still be considered when interpreting the results and could be more thoroughly integrated into future studies for a better understanding of individual variability. SP's IQ (107; superior verbal IQ) differed from the other patients and was the only participants with AgCC with normal performance in both tasks. MD (IQ not assessed) has a university degree; her IQ can also be considered similar to control participants. She displayed normal performance for localization of olfactory-trigeminal stimuli but had the best score for pure olfactory localization of all participants, including controls. Thus, the two participants from the patient group with IQs comparable to those of the controls demonstrated normal or even above-average performance on the tasks. Finally, our study focused solely on localization tasks and did not include other olfactory assessments, such as threshold or identification, which could provide a more comprehensive understanding of olfactory processing in individuals with disrupted interhemispheric communication. Future research should aim to include a larger cohort, incorporate a broader range of olfactory tasks, and potentially incorporate neuroimaging data to elucidate the role of subcortical commissures and neural mechanisms underlying peripheral olfactory interactions in odor localization and overall olfactory function.

In summary, our findings suggest that the CC plays a critical role in interhemispheric communication for both olfactory and trigeminal processing, with the absence of the CC leading to varied effects in localization abilities. The AC and other subcortical commissures may provide compensatory pathways, but further research is needed to understand their exact contributions. The potential for within-hemisphere plasticity and peripheral interactions between sensory systems also warrants deeper investigation to elucidate their roles in chemosensory localization.

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Data availability

The data underlying this article can be shared on request to the corresponding author.

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